REMARKS

Claims 1-17 are pending in this application. No amendments to the claims are considered necessary at this time to deal with the priority issue (and resulting 35 USC 102 rejection) given the results of the telephonic interview with the Examiner on October 17, 2003. During that telephonic interview the Examiner indicated that a document filed prior to the abandonment of copending application serial number 09/415,899, filed 10/8/1999, amended that application's claim of priority to include a claim of priority to application serial number 08/486,549, filed 6/7/1995, which was copending with application serial number 09/415,899. This, according to the Examiner and her quality control supervisor, properly provided a basis to claim priority to the earlier application, the claim to which was denied in the Office communication dated 09/10/2003.

In addition to the above-described basis for the claim of priority, Applicant also provides an alternative basis for the priority claim in the *Priority* section below.

However, claims are amended herein to address the Examiner's concern with what was stated as "vague and indefinite . . . recitation of "gene."" This is believed to clarify, and not narrow, the scope of the claims.

Also, Applicant respectfully requests a notation of correction as follows. On close review, Applicant notes that the "final" version of the rewritten first paragraph of the specification, as provided in the Preliminary Amendment filed with the application on 10/17/2001, is correct. However, the marked-up version contains an error – the serial number corresponding to U.S. patent 6,120,764 is incorrect. Also, as noted below, the last sentence of the original first paragraph, which incorporates by reference the priority-claimed applications, was inadvertently omitted from the marked-up version. Appropriate notation of these errors is requested.

Drawings

Figure 6B was inadvertently omitted in the filing of this application, but this figure is present in application serial number 08/486,549, filed 6/7/1995, to which priority is claimed. This figure is not essential to the enablement or other requirements of the present invention, but its inclusion in a final patent is preferred. The Examiner has informed the Applicants that Fig. 6B cannot be incorporated by reference because the present application "does not include an incorporation by reference of the parent applications." While it is true that no incorporation by reference statement is found in the paragraph added by Preliminary Amendment, Applicant notes that the original first paragraph of application does include the sentence, "All applications for which priority is claimed are hereby incorporated by reference." This sentence was not explicitly deleted, as shown by its non-presence in the marked-up version of the Preliminary Amendment. Applicant respectfully requests reconsideration of the decision to not include Fig. 6B, and also respectfully requests entry of the corrected first paragraph as provided herein.

Priority

As indicated above in the Remarks section, the Examiner has indicated that the document filed 10/09/2001 (Supplemental Oath/Declaration) in application serial number 09/415,899, filed 10/8/1999, which claims priority to application serial number 08/486,549, filed 6/7/1995, is adequate to establish a valid claim to priority for the present application to application serial number 08/486,549, filed 6/7/1995.

In the alternative to the above-indicated basis for a claim to priority to application serial number 08/486,549, filed 6/7/1995, Applicant provides the following reasoning:

A key to the meaning of 35 USC 120 as to a proper priority claims is what is the meaning of ". . . or an application similarly entitled to the benefit of the filing date of the first application, . . . ".

It is advocated that the present application, 09/981,685, is "similarly entitled" to the benefit of 08/486,549 because:

1. The intervening application, 09/415,899, contains, on the basis of incorporation by reference, the entire specification and claims of 08/486,549 as the latter was filed.
2. As such, both 08/486,549 and 09/981,685 (the present application) contain subject matter to support claims in 09/981,685 ". . . in the manner provided by [section 112/1]." I.e., enablement and written description requirements are satisfied in the earliest application.
3. As such, the present application's claim to priority is proper <u>even if</u> there was no need for the intervening application, 09/415,899, to claim priority to 08/486,549. It has been stated that the claiming of priority by this intervening application, 09/415,899, would be proper only if it contained claims for which 08/486,549 provided an enabling disclosure. Such was not the case (see Note below). It is believed that this claiming of priority by an intervening application is properly viewed as a separate issue from the validity of the present claim for priority to an earlier application which was incorporated in its entirety in an intervening, copending application (where the earliest and the present application were not copending).
4. As to "it" in 35 USC 120's ". . . and if it contains or is amended to contain a specific reference to the earlier filed application" refers to the present application.

<u>Note</u>: If the above reasoning is not correct, what happens if an Applicant files a CIP in which the claims are only directed to the new subject matter? A claim of priority to the parent in this series would not be proper. Yet if the Applicant, after the parent issued but before the issuance of the CIP, wanted to pursue additional claims based on the subject matter of the parent, could he/she not pursue such claims in a

continuation of the CIP? It seems that the reasoning is similar here, and that the inability to do this (which seems routine to a patent practitioner) would prejudice the applicants in many cases.

Further to the above reasoning, please see *Ex parte Maziere*, 27 USPQ 2d, 1705 (B.P.A.I. 1993).

Sequence Compliance

In order to provide a complete response to the Notice requirement to comply with the requirements of 37 C.F.R. 1.821-1.825, Applicant has provided a sequence listing (paper and CD), and has amended the paragraph starting on page 4, line 16, to indicate the sequence ID numbers. It is noted that although the paragraph indicating inclusion of a sequence listing appeared in the application as filed, Applicant's records indicate that no such sequence listing was provided. In accordance with this, the enclosed sequence listings are the initial listings.

The following statements are provided with regard to the provided Sequence Listing.

Provided with this Response is a written copy of the "Sequence Listing" for this Application in accordance with 37 C.F.R. 1.821(c). Also provided is a computer readable format copy of the "Sequence Listing" on a properly identified compact disc.

The claims as filed comply with 37 C.F.R. 1.821(d).

The Applicant states that the paper copy of the "Sequence Listing" in the present application is identical to the computer readable copy enclosed herewith. This is in accordance with 37 C.F.R. 1.821(e).

The Applicant states that no new matter is introduced with the submission of the sequence listing.

Should the U.S. Patent Office find that any requirement has not been fully and properly met, it is respectfully requested that the Attorney indicated below be contacted by telephone and provided an opportunity to fully comply with all requirements under 37 C.F.R. 1.821-1.825.

Claim Rejections - 35 USC § 112, second paragraph

Claims 1-17 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

As to the first basis for rejection under 35 USC §112, second paragraph, Applicant, upon review of the claims, believes that the term "gene" is consistent with the definition provided in the specification, page 9, lines 11-12, "[while not intending to be limiting], the term "gene" includes cDNAs, RNA, or other polynucleotides that encode gene products." The specification amply demonstrates that the gene product of an inserted gene is expressed under appropriate conditions. It is axiomatic that expression of a particular gene of interest typically requires that gene being operably linked to a promoter and to other control sequence(s). Accordingly, the present use of the term in the specification and in the claims, in the Applicant's view, is not a source of vagueness nor indefiniteness.

Despite the above, to advance the application to issue, the Applicant has amended the claims herein to further clarify the use of the terms "gene" and "coding sequence," and to thereby eliminate this basis for rejection. As part of this amendment, the term "expression cassette" is added to certain claims. This term is well known in the art, and is used in the specification in connection with the invention, for example, on page 15, line 27. It is emphasized that Applicant's view is that the claims as filed, without the present amendments, are neither vague nor indefinite, and provide the same scope of coverage as the presently amended claims.

As to the second basis for rejection under 35 USC §112, second paragraph, the Examiner has stated that

> "[c]laims 2 and 3 are vague and indefinite in their recitation of the terms "operably linked to target sites" (claim 2) and "target sites operably linked to the gene" (claim 3). It is not clear what is intended by this term, since these target sites <u>have no function</u>

except as a target for recombination action of a recombinase, and would function as such independent of orientation or location." (underline emphasis added)

As to this basis for rejection, it is first noted that the specification, page 12, lines 12-13, states, "The DNA sequences are expressed in hosts after the sequences have been operably linked to (i.e., positioned to ensure the functioning of) an expression control sequence." From this, it is clear that "operably linked" may be seen to mean "positioned to ensure the functioning of" when such functioning is desired.

In contrast to the underlined phrase above, the recombinase target sites, as used in the present invention, are shown to act in a way to control expression of a gene/coding sequence that is, for instance, positioned between that gene/coding sequence and a promoter. In one such embodiment, excess nucleotides are present between two recombinase target sites, such that without action of a recombinase to remove one site and the excess nucleotides, the promoter is not properly positioned in relation to the coding sequence to obtain desired expression level of the latter (See Example 5, starting on page 19, and particularly page 19, line 12 to page 20, line 17). This is but one of many strategies using recombinase target sites and the corresponding recombinase to effectuate a "molecular switch" such as is disclosed and claimed in the present application (See, for example, page 26, line 7, to page 27, line 22).

It also is noted that the ways in which the particular Cre/loxP recombinase/recombinase target sites are known to operate is described on page 2, lines 3-13. In particular, is it clear that the recombinase target sites, when positioned as described in the specification, do have a function beyond being a target for a recombinase, and, further, the relative orientation of two nearby recombinase target sites is relevant to the outcome of recombination.

Thus, it is believed that the terms "operably linked to target sites" (claim 2) and "target sites operably linked to the gene" (claim 3) are acceptable in view of the purposes for such sites that are demonstrated and discussed in the specification. In view of the above, reconsideration of the

basis for rejection based on the above quote is respectfully requested. However, if the Examiner is not persuaded by the above, Applicant is willing to later amend these claims to replace "operably linked to" with "operably controlled by."

As to the third and last basis for rejection under 35 USC §112, second paragraph, the Examiner has stated that claims 3-17 are vague and indefinite, in essence, because the stated change in expression is not clearly associated with a stated standard or basal level of expression. Applicant concurs that the expression level from which a comparison is made is the expression level that was present prior to the recombination event described in the respective claim. Applicant is of the view that the specification and the claims, as written, make this sufficiently clear such that no addition of "compared to the expression level that was present prior to said recombination" is required. This is clear, *inter alia*, from the meaning of the joining terms "whereby," "resulting in," "alters," and the like.

Therefore, reconsideration of this basis for rejection is respectfully requested. Applicant is willing to later amend these claims, but does not consider this necessary.

The above claim amendments are made to more clearly express the subject of the claims, do not add new matter, and do not narrow the claims.

Claim Rejections - 35 USC § 102

Claims 1-3, 8 and 9 stand rejected under 35 USC § 102 as being anticipated by Anton et al. (J. Virology: 69(8), pp. 4600-4606, 1995).

Claims 1-3, 8 and 9 also stand rejected under 35 USC § 102 as being anticipated by Kanagae et al. (Nucleic Acids Research 23(19), pp. 3816-3821, 1995).

Based on the proper claim of priority to application serial number 08/486,549, filed 6/7/1995, the Anton et al. and the Kanagae et al. references are not prior art references, and these rejections should be withdrawn. Reconsideration and withdrawal of these rejections is respectfully requested.

Claim Rejections - 35 USC § 103

Claims 1-17 stand rejected under 35 USC § 103(a) as being unpatentable over Sauer (US Patent No.: 4,959,317) in view of Berkner (Curr. Top. Microbiol. Immunol., 158:39-66, 1992).

In this obviousness rejection, the Office action notes that the Sauer reference "discloses that any vector may be used, including viruses (column 4, lines 33-35)." This is found early in the patent, and no specific listing of vector types or viruses is provided. The Office action goes on to acknowledge that "the reference does not teach adenoviruses containing a gene under the control of a recombinase, or an adenovirus containing a promoter flanked by recombinase target sites which, upon expression of the recombinase, is inverted or deleted depending on the orientation of the target sites." (page 8 of Office action, underline emphasis added)

First, Sauer's disclosure that "any vector may be used" must be taken in context with regard to 1) the great diversity among families of viruses, 2) uncertainties in applying technology demonstrated in one virus belonging to one group to all other viruses in all other virus groups, and 3) the enablement requirements of the U.S. Patent Office for biotechnology-based inventions. On its surface, Sauer's disclosure that "any vector may be used" is akin to stating that a particular invention cover "all organisms" when there is inadequate teaching of the invention for "all organisms." The Sauer invention's focus is on use of Cre recombinase in eukaryotic cells, and the inventors are merely stating that any vector, including viruses in general, could be used to practice the invention. In fact, the Sauer patent focuses on specific and limited embodiments that are not pertinent to adenovirus-based inventions such as the present invention.

Further, the teachings of Sauer do not overcome the unpredictability in the art, and more particularly, the unpredictability of whether what Sauer discloses for pseudorabies virus and certain eukaryotic cells would work with adenoviruses. The proper standard is "obvious" and not "obvious to try." Here, as one example, it was unknown, and unpredictable, whether the adenovirus enzymes would tolerate the presence of a palindromic lox sequence that would remain after Cre excision of a particular sequence, i.e., a spacer sequence, such that expression of the inserted gene would occur. In particular, see the specification, page 16, lines 2-7 and 25-27 (stating, in part, ". . . it could not be predicted that the luciferase could be expressed following excision of the spacer by Cre mediated recombination. . . . Isolation of such a vector would confirm that Ad5 could tolerate the palindromic *loxP* sequence in addition to the terminal inverted repeats.").

It also was uncertain whether, in an adenovirus, a spacer flanked by loxP sites would in fact block expression of an inserted gene of interest (such as luciferase in the examples in the specification). This spacer with loxP sites was shown in to block expression in Example 5 (see page 20, lines 5-8). Given the tendency of adenovirus to spontaneously recombine, it also was uncertain whether a high frequency of spontaneous recombination between repeated loxP sites might occur, resulting in a wide range of undesired, contaminating species that would render the approach useless. As indicated in Example 5 (page 21, lines 9-12), a small amount of such spontaneous recombination, in the absence of Cre, did occur, but this was manageable and did not render the method useless. Thus, it is incorrect to state there was a realistic expectation of success of achieving the results in a wide range of viruses, and in the instant case, of adenoviruses, given unpredictability in applicability of a method across such a wide range of diverse organisms as virus families.

Further, Applicant respectfully states that the Sauer reference lacks a specific motivation or suggestion to modify (i.e., to use with an adenovirus), or to be combined with Berkner or other references that disclose the use of adenoviruses as vectors. This is because, in large part, Sauer

cannot be properly viewed to disclose adenoviruses in its overly broad ". . . any vector may be used, including viruses . . . " statement. Therefore, it was not obvious to place the features described in the Sauer reference in an adenovirus vector, such as is done in the present invention. Lacking such specific motivation or suggestion, and in view of the unpredictability of applying Sauer across the wide range of viruses and their replication enzymes, it is unpermissible hindsight to combine Sauer with Berkner or other adenoviruses references. That is, even in view of Sauer, at the time of the present invention it was unknown and unpredictable as to whether particular, key adenoviral enzymes would function when one or more target sites for a non-adenoviral recombinase enzyme was inserted in the nucleotide sequence of the adenovirus.

Further, there is no evidence that Sauer's disclosure, as a whole, is enabling with regard to adenovirus vectors. ("In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." Motorola, Inc. v Interdigital Technology, 121 F.3d 1461, 1471 (Fed. Cir. 1997), quoting Beckman Instruments, Inc., v. LKB Produkter AB, 892 F.2d, 1547, 1551). Sauer makes no reference nor showing that the methods applied to pseudorabies virus work in adenoviruses, and Berkner, not having disclosed such methods, likewise is non-enabling for adenoviruses. This provides an additional basis for withdrawing the noted obviousness rejection.

In conclusion, for the reasons provided above, the obvious rejection is improper. Reconsideration is respectfully requested.

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All claims having been placed in condition for allowance, expedited passage of this case to issuance is respectfully solicited.

Applicant requests that the Examiner call the undersigned if clarification is needed on any aspect of this response, or if the Examiner believes that any valid basis of non-patentability

remains after entrance and consideration of the remarks and amendments presented herein.

Respectfully submitted,

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